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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,126	04/16/2001	Randolph J. Noelle	20052/1200522-US1	4674

7278 7590 01/15/2008
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EXAMINER

GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
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1644

MAIL DATE	DELIVERY MODE
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01/15/2008

PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RANDOLPH J. NOELLE, BRUCE R. BLAZAR, DANIEL A.
VALLERA and PATRICIA A. TAYLOR

Appeal 2008-0011¹
Application 09/835,126
Technology Center 1600

Decided: January 15, 2008

Before, TONI R. SCHEINER, DEMETRA J. MILLS, and
ERIC GRIMES, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for new matter and for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Claim 1 is representative.

¹ This case is related to Appeal 2007-4358, Application 09/951,537 handled concurrently with this appeal.

1. A method for inducing T-cell tolerance or non-responsiveness of donor T-cells to desired alloantigen-bearing cells *ex vivo* comprising the following:

- (i) purifying CD4⁺ T-cells from donor tissue;
- (ii) irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T cells;
- (iii) producing a mixed lymphocyte reaction culture comprising the purified donor CD4⁺ T-cells and irradiated, T-cell depleted alloantigen-bearing cells obtained from a recipient;
- (iv) adding an anti-gp39 antibody to the culture, thereby initiating a mixed lymphocyte reaction culture comprising purified donor CD4⁺ T-cells, T-cell depleted recipient alloantigen-bearing cells, and anti-gp39 antibody;
- (v) maintaining the mixed lymphocyte reaction culture *ex vivo* for a sufficient time to render the donor CD4⁺ T-cells substantially tolerant or non-responsive to said alloantigen-bearing cells; and
- (vi) assaying *ex vivo* for induction of donor CD4⁺ T-cell tolerance or non-responsiveness.

Cited References

Ochoa	US 5,725,855	Mar. 10, 1998
Noelle	US 5,876,718	Mar. 2, 1999
Rooney	US 5,962,318	Oct. 5, 1999
Sykes	US 6,006,752	Dec. 28, 1999

Knulst et al., "Improved survival from potentially lethal graft-vs.-host disease by donor pretreatment with a recipient-specific blood transfusion. II.

Evidence for a principal role of the CD4⁺T cell subset,” 23 Eur J. Immunol. 299-302 (1993) (hereafter “Knulst”).

Riddell et al., “The use of anti-CD3 and anti-CD28 monoclonal antibodies to clone and expand human antigen-specific T cells,” 128 J. of Immunological Methods 189-201 (1990) (hereafter “Riddell”).

Grounds of Rejection

Claims 1, 2, 4-11 and 13 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description (new matter).

Claims 1, 2, 4-7, 10-11 and 13 stand rejected under 35 U.S.C. § 103 as obvious over Noelle and Rooney in view of Riddell, Sykes, Ochoa and Knulst.

DISCUSSION

Background

“Methods of treating transplanted tissue or organs (allogeneic or xenogeneic) *ex vivo* in order to tolerize T-cells contained therein to donor antigens (xenoantigens or alloantigens) are provided. The treated tissue or organ can be transplanted in a recipient with reduced risk of graft-versus-host disease.” (Specification 1.)

New Matter

Claims 1, 2, 4-11 and 13 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description (new matter).

The Examiner contends that

The specification as originally filed does not provide support for the invention as now claimed:

(i) “purifying CD4⁺ T cells from donor tissue” as well as steps recited in claim I (iii)(iv)(v)(vi), as they read on “purified donor CD4⁺ T cells/T cell tolerance”

(Answer 5.)

With respect to the step of purifying CD4⁺ T cells from donor tissue, Appellants contend that

the claim terms are clearly supported by the present specification because the present specification provides numerous examples that explain to those skilled in the art the meaning of the terms “purifying CD4⁺ T-cells from donor tissue” and “purified donor CD4⁺ T-cells/T-cell tolerance” as this term is used in steps (iii)-(vi) of claim 1.

The specification specifically discloses that “highly purified CD4⁺ lymph node T cells” are used as part of the MLR of Example 1 (specification, page 10, lines 26-28). Products from the MLR containing purified CD4⁺ T cells of Example 1 are then integrated or compared in each of Examples 2-10. Accordingly, all the results obtained and discussed with regard to the ten Examples provided in the specification are based on the use of CD4⁺ T-cells purified from donor tissue (specification, Examples 1-10, at page 10, line 25 - page 14, line 29).

(Br. 5-6.)

The purpose of the written description requirement is to “ensure that the scope of the right to exclude, as set forth in the claims does not overreach the scope of the inventor’s contribution to the field of art far as described in the patent specification.” *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). To that end, to satisfy the written description

requirement, the inventor “must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention”. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). “One shows that one is ‘in possession’ of the invention by describing the invention, with all its claimed limitations”. *Lockwood v. American Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphases in original).

We agree with Appellants and find that Example 1 of the Specification pages 10-11, as originally filed, provides support for a step of purifying CD4⁺ T-cells from donor tissue. In particular, the Specification describes that “highly purified CD4⁺ lymph node T cells from C.H2^{bm12} were plated ... in microtiter wells or in bulk culture in 24-well plates.” (Specification 10: 28-30.) While we acknowledge that the original claims in the application were directed to a method for inducing T-cell tolerance in vitro in donor tissue containing CD4⁺ T-cells, and that the claims have been modified from their original presentation to recite an ex vivo method of inducing and assaying for tolerance in purified CD4⁺ T-cells, we find that the present claims including a step of purifying CD4⁺ T-cells from donor tissue also find support in the Specification as originally filed, particularly in Example 1.

Thus, we reverse the rejection of the claims for new matter with respect to the phrase “purifying CD4⁺ T-cells from donor tissue”.

The Examiner also argues the time period of 6 to 10 days in claim 7 is not supported by the Specification as originally filed.

(Answer 5-6.)

Appellants argue that

[t]he specification discloses that “the culture will be maintained for a time sufficient to induce T-cell tolerance” and that “[t]ypically, this time will range from about 1-2 days to 30 days, more typically about 5-15 days, and most typically about 10 days” (specification, page 8, lines 27- 29). Further, Example 4 provides that the MLR was maintained for a “ten day cell culture period” (specification, page 12, line 2). One skilled in the art could readily derive the claimed ranges from the disclosure provided. Also, the claim term “for a time ranging from about 5 to 30 days” is flexible due to inclusion of the word “about.”

(Br. 8.)

It is the Examiner’s “initial burden [to] present[] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims”. *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). The proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an Applicant from adding information that goes beyond the subject matter originally filed. *In re Rasmussen*, 650 F.2d 1212, 1214 (CCPA 1981).

We do not find that the Examiner has provided evidence or reasons why persons skilled in the art would not recognize in the Specification’s disclosure of time period within the range of “about 5-15 days, and most typically about 10 days,” a description of the culture time period of 6-10 days as defined by the claims. The written description rejection of the claims for new matter is reversed.

Obviousness

Claims 1, 2, 4-7, 10-11 and 13 stand rejected under 35 U.S.C.
§ 103 as obvious over Noelle and Rooney in view of Riddell, Sykes, Ochoa
and Knulst.

The Examiner contends that

Noelle et al. teach inducing T cell non-responsiveness to
desired alloantigens with gp39 antagonists, including the use of
anti-gp39 antibodies (i.e. anti-CD40L antibodies) (*gp39
Antagonists* on columns 5-9) and antigen presenting cells,
including bone marrow and peripheral bloods cells (*Cells of
Induction of Antigen-Specific Tolerance* on columns 9-11), for
transplantation, including bone marrow transplantation,
including reliance upon in vitro / ex vivo manipulations of cells
prior to transfer to the transplant recipient (*Administration of
Cells and gp39 Antagonists and Uses of the Methods of the
Invention* on columns 9-13) ...

...

While Noelle et al. teaches the reactivity of anti-gp39
antibodies on T cells, including CD4⁺ T cells, and teaches the
isolation and ex vivo treatment of bone marrow cells (see
Examples), Noelle et al. does not teach explicitly the
purification and testing of isolated CD4⁺ T cells in a mixed
lymphocyte reaction (MLR) under the conditions claimed per
se.

(Answer 7-8.)

The Examiner further acknowledges that Noelle does not teach
purification and testing of isolated CD4⁺ T cells in a mixed
lymphocyte reaction (MLR) (Answer 8), that Noelle is silent about
particular time ranges cited in the claims (Answer 8); that Noelle does
not explicitly disclose monitoring or assaying ex vivo donor T cell

tolerance or non-responsiveness (Answer 9); and that Noelle does not teach standard procedures for manipulating lymphocyte populations (Answer 9). However, the Examiner relies on multiple prior art patents and publications including Sykes, Rooney, Ochoa, Ridell, and Knulst for the “well known, standard and common applications” in the art with respect to the subject matter missing from Noelle. (Answer 18.)

We conclude that the Examiner has not presented sufficient evidence to support a prima facie case of obviousness. The Examiner argues that Noelle was not limited to in vivo administration of anti-gp39 antibodies (Answer 19) and indicates that Noelle provided teachings to target CD4⁺ helper cells in the ex vivo manipulation to induce tolerance or antigen-specific unresponsiveness. (Answer 22.) Noelle, col. 22, ll. 51-60, indicates that “anti-gp39 interferes with the ability of T-cells to elicit a strong GVHD clinical immunopathology and splenomegaly [and] that the antibody administration elicits unresponsiveness on the CD4⁺ subpopulation.” This disclosure however, does not provide motivation for purifying the CD4⁺ T-cells and using them in a mixed lymphocyte assay.

Noelle discloses that *bone marrow* (not CD4⁺ T cells) can be tolerized ex vivo before transfer to the recipient host by incubating the donor bone marrow with B cells from the host and a gp39 antagonist in vitro. Thus, Noelle’s ex vivo example is in the context of marrow transplantation and provides no apparent reason why one of ordinary skill in the art would purify CD4⁺ T-cells from bone marrow or tissue intended for transplantation, and then tolerize them.

In making an obviousness determination over a combination of prior art references, it is important to identify a reason why persons of ordinary skill in the art would have attempted to make the claimed subject matter. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). When making such a determination, the scope of the prior art and level of ordinary skill must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Examiner provides no evidence or articulated reasoning as to why one of ordinary skill in the art would purify isolated CD4⁺ T-cells in view of the ex vivo example using bone marrow in Noelle.

Claim 1 recites steps for performing an assay of donor CD4⁺ T-cells to determine whether they have developed tolerance or unresponsiveness upon a mixed lymphocyte reaction with anti-gp39 antibody. Such an assay is not suggested by Noelle's disclosure of an ex vivo bone marrow transplantation involving a mixed lymphocyte reaction. We find none of the secondary references make up for this deficiency in Noelle.

In view of the above, the rejection of the claims for obviousness is reversed.

SUMMARY

The rejection of claims 1, 2, 4-11 and 13 under 35 U.S.C. § 112, first paragraph for lack of written description (new matter) is reversed.

The rejection of claims 1, 2, 4-7, 10-11 and 13 under 35 U.S.C. § 103 as obvious over Noelle and Rooney in view of Riddell, Sykes, Ochoa and Knulst is reversed.

Appeal 2008-0011
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REVERSED

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